

Use of bioluminescent imaging to assay the transplantation of immortalized human fetal hepatocytes into mice.

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Public Summary:

Scientific Abstract:

Noninvasive serial monitoring of the fate of transplanted cells would be invaluable to evaluate the potential therapeutic use of human hepatocyte transplantation. Therefore, we assessed the feasibility of bioluminescent imaging using double or triple fusion lentiviral vectors in a NOD-SCID mouse model transplanted with immortalized human fetal hepatocytes. Lentiviral vectors driven by the CMV promoter were constructed carrying reporter genes: firefly luciferase and green fluorescence protein with or without herpes simplex virus type 1 thymidine kinase. Human fetal hepatocytes immortalized by telomerase reconstitution (FH-hTERT) were successfully transduced with either of these fusion vectors. Two million stably transduced cells selected by fluorescence-activated cell sorting were injected into the spleens of NOD-SCID mice pretreated with methylcholanthrene and monocrotaline. The transplanted mice were serially imaged with a bioluminescence charged-coupled device camera after D-luciferin injection. Bioluminescence signal intensity was highest on day 3 ($6.10 \pm 2.02 \times 10^5$ p/s/cm²/sr, mean \pm SEM), but decreased to $2.26 \pm 1.54 \times 10^5$ and $7.47 \pm 3.09 \times 10^4$ p/s/cm²/sr on day 7 and 10, respectively ($p = 0.001$). ELISA for human albumin in mice sera showed that levels were similar to those of control mice on day 2 (3.25 ± 0.92 vs. 2.84 ± 0.59 ng/ml, mean \pm SEM), peaked at 18.04 ± 3.11 ng/ml on day 7, and decreased to 8.93 ± 1.40 and 3.54 ± 0.87 ng/ml on day 14 and 21, respectively ($p = 0.02$). Real-time quantitative RT-PCR showed gene expression levels of human albumin, alpha1-antitrypsin, and transferrin in mouse liver were $60.7 \pm 6.5\%$, $26.0 \pm 1.4\%$, and $156.8 \pm 62.4\%$ of those of primary human adult hepatocytes, respectively, and immunohistochemistry revealed cells with human albumin and alpha1-antitrypsin expression in the mouse liver. In conclusion, our study demonstrated that bioluminescent imaging appears to be a sensitive, noninvasive modality for serial monitoring of transplanted hepatic stem cells.

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